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Session 6: Actual Applications and Future Perspectives of Dual ETA/ETB Antagonists

Benefits of dual endothelin receptor antagonists: Mechanisms of action, current studies, and future directions

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Over expression of endothelin (ET) and its receptors ETA and ETB results in pathological changes including hypertrophy and fibrosis. These changes are hallmarks of conditions such as pulmonary arterial hypertension (PAH). Dual, but not single (ETA) endothelin receptor antagonists (ERAs), have been shown to improve survival in animal models of pulmonary hypertension and chronic heart failure. Hyperstimulation of ETB receptors following ETA receptor blockade by single ERAs leads to increased vascular permeability and fluid retention. These observations support the rationale that dual receptor antagonism may have optimal efficacy and minimized risk of edema. Macitentan is a novel dual ERA designed for optimized physicochemical properties, favoring sustained receptor binding and enhanced tissue penetration. Macitentan does not increase bile salts, the proposed underlying mechanism for elevated liver enzymes observed with the dual ERA bosentan. Macitentan was studied in the Phase III SERAPHIN trial, the first event-driven, outcome trial in PAH. The study included over 740 patients. Macitentan 10 mg reduced the risk of morbidity and mortality by 45% versus placebo. Moreover, there was no difference in incidence of peripheral edema or liver enzyme elevations between placebo and macitentan-treated patients. Current preclinical and clinical research on the ET system highlights the potential for dual ERAs in other diseases. Future directions may include the fields of scleroderma, pulmonary fibrosis, heart diseases and oncology.

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Effects of bosentan on digital ulcers in patients with systemic sclerosis

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Systemic sclerosis (SSc) is a connective tissue disease involving tissue fibrosis and endothelial injury. In the 1990s, several studies indicated that plasma endothelin (ET)-1 was elevated in patients with SSc, which might contribute to endothelial injuries (i.e.: Raynaud's phenomenon, digital ulcer, pulmonary hypertension, renal dysfunction). Interestingly, ET-1 exerted a fibrotic effect inducing collagen production in skin fibroblasts, suggesting that ET-1 might be involved in both tissue fibrosis and endothelial injury in patients with SSc. Digital ulcer in patients with SSc results from peripheral vascular damage which related to an excessive vasoconstriction. That may be refractory for the treatment with any prostanoids. The ability of vasodilation in prostanoids could be almost equivalent to that in endothelin receptor antagonist (ERA). However, prostanoids could not exhibit anti-fibrotic properties, which may be different from the effects of ERA. In this session, I am going to show the effects of bosentan on digital ulcers in patients with SSc and to evaluate the inhibitory effects of bosentan on the fibrogenic responses through TGF- β in SSc fibroblasts.

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